S 44. *The Synthesis of Thyroxine and Related Substances. Part III. The Synthesis of Thyroxine from 2 : 6-Dinitrodiphenyl Ethers.*

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A synthesis of thyroxine in an overall yield of 14% is described, beginning with *p*-hydroxybenzaldehyde and proceeding *via* a 2 : 6-dinitrodiphenyl ether. Variations of this scheme, all following essentially similar routes, have been studied and are outlined.

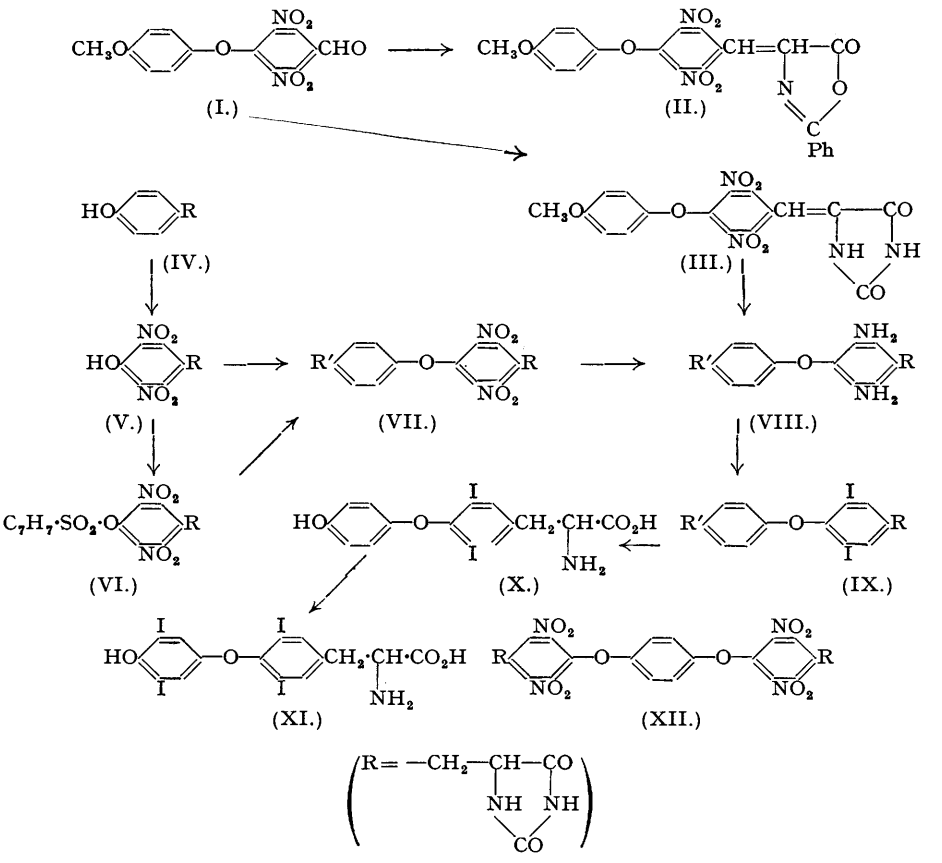
It was demonstrated in Part I (this vol., p. S 187) that 2 : 6-diaminodiphenyl ethers can be tetrazotised and that iodine atoms can be substituted for the diazo-groups by means of the Sandmeyer reaction. 3 : 5-Di-iodo-4-(4′-methoxyphenoxy)benzaldehyde was prepared and condensed with hippuric acid to give 2-phenyl-4-(3′ : 5′-di-iodo-4′-*p*-methoxyphenoxybenzylidene)oxazol-5-one, a compound previously obtained by Harington and Barger (*Biochem. J.*, 1927, **21**, 169) by a different route, and this could be converted into thyroxine by the known method. As the yield of the above aldehyde was unsatisfactory, an attempt was made to prepare this oxazolone beginning with 3 : 5-dinitro-4-(4′-methoxyphenoxy)benzaldehyde (I), an intermediate readily available by the methods described in Part II. The oxazolone (II), prepared from (I) in the usual manner, was reduced catalytically in glacial acetic acid solution, 10% palladised charcoal being used as catalyst. The uptake of hydrogen indicated that saturation of the ethylenic linkage, as well as reduction of both nitro-groups, had taken place, but all attempts to isolate the diamine as such or as a salt proved unsuccessful, the materials being extremely unstable and deteriorating rapidly. Furthermore, tetrazotisation by addition of the freshly prepared diamine solution to a solution of nitrosylsulphuric acid and treatment of the mixture with iodide solution proved equally unpromising, no di-iodo-compound being isolated.

Attention was then directed to the condensation of the aldehyde (I) with hydantoin, morpholine being used as the catalyst, this base having proved useful for the similar condensation with *p*-hydroxybenzaldehyde (Part I). Although a reaction appeared to occur, unchanged hydantoin was recovered, and it was found that the diphenyl ether (I) was readily cleaved by morpholine to give 3 : 5-*dinitro*-4-*morpholinobenzaldehyde*, a characteristic instability exhibited by polynitrodiphenyl ethers (Ungnade, *Chem. Reviews*, 1946, **38**, 413).

For similar reasons other bases were unsuitable as condensing agents. Condensation under acid conditions was more successful; the hydantoin (III) was prepared in 20% yield in glacial acetic acid containing sodium acetate, though only very poor yields were obtained with zinc chloride as catalyst. The hydantoin (III) could be reduced catalytically to 5-(3′ : 5′-diamino-4′-*p*-methoxyphenoxybenzyl)hydantoin (VIII; R′ = OMe), which was unstable but could be isolated and characterised as its *monohydrochloride*. The feasibility of this approach established, it was necessary to investigate alternative methods for the preparation of (VIII; R′ = OMe), which could be obtained only in unsatisfactory yield by the above procedure.

A synthesis of thyroxine beginning with tyrosine would have many advantages; one of the most important is the possibility of synthesising L-thyroxine from L-tyrosine, the configurational relationship between the two amino-acids having been proved by Canzanelli, Harington, and Randall (*Biochem. J.*, 1934, **28**, 68). As it was desirable to have a protected alanine side chain in the first instance, the nitration of 5-*p*-hydroxy-benzyl- and -benzylidene-

hydantoins was examined. Nitration of the latter in cold nitric acid containing urea gave a *mononitro*-derivative but further nitration could not be effected, nor did nitration of 5-(4′-*toluene*-p-*sulphonyloxybenzylidene*)*hydantoin* give the required dinitro-compound. Portionwise addition of 5-*p*-hydroxybenzylhydantoin to concentrated nitric acid at 0° yielded mainly 5-(3′-nitro-4′-hydroxybenzyl)hydantoin, but when the nitration was carried out at 25—30°, and the mixture kept at this temperature for two hours, the dinitro-compound (V) was obtained in 83% yield. These compounds were identical with those prepared by Johnson and Kohmann (*Amer. Chem. J.*, 1915, **37**, 1881, 2170) by desulphurization of the thiohydantoins obtained from the corresponding nitrotyrosines.

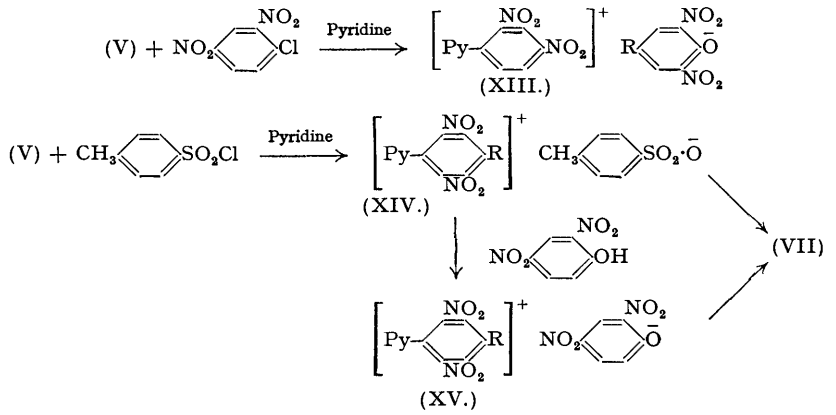


The compound (V) was converted into its *toluene*-p-*sulphonyl derivative* (VI) in the usual manner in dilute alkaline solution, and this ester, when heated with quinol monomethyl ether in pyridine solution, gave 5-(3′ : 5′-*dinitro*-4′-p-*methoxyphenoxybenzyl*)*hydantoin* (VII; R′ = OMe). The pyridinium quaternary salt known to be an intermediate in reactions of this type (see Part II) was not isolated, and it was later found that the isolation of the toluene-*p*-sulphonyl ester was also unnecessary, the required diphenyl ether being obtained directly and in good yield on heating (V) with pyridine, toluene-*p*-sulphonyl chloride, and quinol monomethyl ether; (VII; R′ = OMe), prepared by this method, has proved to be the most convenient intermediate in the synthesis of thyroxine from substituted 2 : 6-dinitrodiphenyl ethers; the corresponding hydroxy-compound (VII; R′ = OH) (see p. S 201) was less satisfactory.

Attempts were also made to replace the hydroxyl group of (V) by chlorine, with a view to condensation with quinol monomethyl ether by the usual Ullmann reaction (cf. Ullmann and Sponagel, *Ber.*, 1905, **38**, 2211), but none of the methods examined was of any avail and the chloro-compound could not be obtained.

The application of quaternary derivatives of type (XIII) to the preparation of diphenyl ethers was described in the preceding paper, but it was found that 1-chloro-2 : 4-dinitrobenzene

reacted with (V) and pyridine to give the quaternary *salt* (XIII), which failed to form a diphenyl ether with quinol monomethyl ether and also failed to give a chloroplatinate. The required quaternary compound (XV) obtained by metathesis between (XIV) and 2 : 4-dinitrophenol yielded the diphenyl ether (VII; R′ = OMe) on treatment with quinol monomethyl ether and readily formed a *chloroplatinate*.



The dinitro-compound (VII; R′ = OMe) was catalytically reduced in the usual manner and the monohydrochloride of the resulting unstable diamine proved to be identical with that of the compound (VIII; R′ = OMe) described above. The diamine was further characterised by preparation of a *triacetyl* derivative. Addition of a solution of the freshly prepared diamine in acetic acid (cf. Hodgson and Walker, *J.*, 1935, 530) or phosphoric acid (cf. Schoutissen, *J. Amer. Chem. Soc.*, 1933, **55**, 4535) to a cooled stirred solution of nitrosylsulphuric acid in concentrated sulphuric acid gave a solution of the tetrazonium compound, which on dropwise addition to a solution of potassium tri-iodide yielded crude 5-(3′ : 5′-*di-iodo*-4′-p-*methoxyphenoxybenzyl*)*hydantoin* (IX; R′ = OMe).

The purification of this material proved laborious, until it was demonstrated that traces of impurities arising in the reduction stage were complicating the isolation. The problem was resolved either by ensuring that complete catalytic reduction was effected by hydrogenation at an elevated temperature in an autoclave or by the use of the isolated diamine hydrochloride. In this way the purification of the di-iodo-compound (IX; R′ = OMe) was greatly simplified and the yield substantially increased. The diamine could also be tetrazotised by treatment with an acetic acid solution of amyl nitrite in concentrated sulphuric acid solution, but the yield of di-iodo-compound (IX; R′ = OMe) was poorer than when nitrosylsulphuric acid was employed. No di-iodo-compound was obtained on treatment of the diamine (VIII; R′ = OMe) in aqueous sulphuric acid with aqueous sodium nitrite and subsequent addition of the mixture to iodide solution.

Demethylation of (IX; R′ = OMe) to 5-(3′ : 5′-*di-iodo*-4′-p-*hydroxyphenoxybenzyl*)*hydantoin* (IX; R′ = OH) was carried out, at first, by refluxing the material with a mixture of acetic acid and 48% hydrobromic acid solution, fission being complete after six hours. Demethylation was also effected in one hour if the hydrobromic acid was replaced by 57% hydriodic acid, and further heating with the latter yielded some 3 : 5-di-iodothyronine (X) as well as (IX; R′ = OH). Since, however, polarographic analysis (cf. Part IV) indicated rupture of the diphenyl ether linkage under these conditions, examination of this method of hydrolysing the hydantoin was not pursued.

A possible simplification of the preparation of (IX; R′ = OH) from (V) would be the use of quinol instead of its monomethyl ether. It was demonstrated in Part II that quinol will form a diphenyl ether when it reacts with the pyridinium quaternary derivative of 3 : 5-dinitro-4-toluene-*p*-sulphonyloxytoluene, and by a parallel procedure (VII; R′ = OH) was readily obtained from (VI), but was accompanied by a small amount of non-phenolic by-product, for which the structure (XII) is suggested. Here again, conversion of (V) into (VII; R′ = OH) could be carried out directly, without isolation of the intermediate toluenesulphonyl ester or quaternary salt. An attempt to prepare (VII; R′ = OMe or OH) by condensation in liquid ammonia as solvent yielded only 5-(3′ : 5′-*dinitro*-4′-*aminobenzyl*)*hydantoin*, the same compound being obtained on treatment of (VII; R′ = OMe or OH) with liquid ammonia. This amine

failed to form a hydrochloride, as might be expected from the presence of two *o*-nitro-groups, and it was characterised by the preparation of its *di-* and *tri-acetyl* derivatives.

Compound (VII; R′ = OH) was reduced catalytically, and the *diamine* (VIII; R′ = OH) was isolated as a stable crystalline compound, containing one molecule of acetic acid of crystallisation, and was characterised by the formation of a *dibenzoyl* derivative. The tetrazotisation and subsequent Sandmeyer reaction proceeded normally to yield a di-iodo-compound (IX; R′ = OH), identical with that obtained by demethylation of (IX; R′ = OMe).

Alkaline hydrolysis by dilute sodium hydroxide solution converted (IX; R′ = OH) into 3 : 5-di-iodothyronine (X), the yield of the latter improving with increase in time of heating, reaching a maximum after 15 hours. Stainless-steel vessels were employed for the hydrolysis, glass vessels being obviously unsuitable, whilst copper caused complete decomposition of the materials.

Originally, Harington and Barger (*Biochem. J.*, 1927, **21**, 169) iodinated 3 : 5-di-iodothyronine (X) by N-iodine solution in concentrated aqueous ammonia, to give thyroxine (XI) in 50% yield. Later (*ibid.*, 1928, **22**, 1429), Harington stated that the yield of thyroxine was increased to 70—80% by employing more concentrated solutions of iodine. In the present authors' experience, however, high yields of (XI), identical in all respects with an authentic specimen, were achieved by using N-iodine solution, thus avoiding the formation of large quantities of nitrogen tri-iodide, which reacts only slowly.

The yield of (XI) from *p*-hydroxybenzaldehyde *via* (VII; R′ = OMe), *i.e.*, by use of quinol monomethyl ether, was 14%.

Experimental.

2-Phenyl-4-(3′ : 5′-dinitro-4′-p-methoxyphenoxybenzylidene)oxazol-5-one.—3 : 5-Dinitro-4-(4′-methoxyphenoxy)benzaldehyde (3 g.), sodium acetate (5 g.), and hippuric acid (1·9 g.) were heated on a steam-bath with acetic anhydride (15 ml.) for 15 minutes. The mixture was cooled, diluted with water, and kept until excess of acetic anhydride was destroyed. The solid was filtered off, dried, and crystallised from benzene–ethyl alcohol, forming bright yellow needles, m. p. 194° (2 g.; 45%) (Found: C, 60·0; H, 3·5; N, 8·8. $C_{23}H_{15}O_8N_3$ requires C, 59·9; H, 3·3; N, 9·1%).

The corresponding *benzylidenehydantoin* was obtained when the above aldehyde (2 g.), hydantoin (0·7 g.), sodium acetate (2·5 g.), glacial acetic acid (20 ml.), and acetic anhydride (3 drops) were heated under reflux for 3 hours and the cooled mixture diluted with water (20 ml.). After standing for some hours, the deposited crystals were filtered off and crystallised from glacial acetic acid, giving pale yellow needles, m. p. 290° (0·5 g.; 20%) (Found: C, 50·7; H, 3·0; N, 13·6. $C_{17}H_{12}O_8N_4$ requires C, 50·1; H, 3·0; N, 14·0%).

3 : 5-Dinitro-4-morpholinobenzaldehyde.—3 : 5-Dinitro-4-(4′-methoxyphenoxy)benzaldehyde (0·5 g.) was treated with morpholine (1 ml.), an exothermic reaction setting in. The mixture was heated for a short time on the water-bath, and the cooled reaction mixture treated with dilute hydrochloric acid. The insoluble green solid was crystallised from glacial acetic acid, forming yellow needles, m. p. 148—149° (Found: C, 47·2; H, 4·0; N, 14·3. $C_{11}H_{11}O_6N_3$ requires C, 46·8; H, 3·9; N, 15·0%).

5-(3′-Nitro-4′-hydroxybenzylidene)hydantoin.—5-4′-Hydroxybenzylidenehydantoin (5 g.) was added to a stirred solution of nitric acid (50 ml.) containing a little urea, while the temperature was kept at 15°. An immediate yellow precipitate formed and the mixture was poured into a large volume of ice-water. The precipitate was filtered off, washed with water, dried, and recrystallised from a large volume of tetrachloroethane, giving a yellow powder (2 g., 33%), m. p. 318°. It could also be crystallised from 50% acetic acid (Found: C, 48·6; H, 2·9; N, 16·8. $C_{10}H_7O_5N_3$ requires C, 48·1; H, 2·8; N, 16·9%).

5-Toluene-p-sulphonyloxybenzylidenehydantoin.—5-4′-Hydroxybenzylidenehydantoin (1 g.) was suspended in water (10 ml.) containing toluene-*p*-sulphonyl chloride (0·93 g.). The mixture was heated on the steam-bath while sodium carbonate (0·26 g.) was added in small portions. A white precipitate formed and the heating was continued for a further 2 hours. After cooling, the precipitate was filtered off, washed with water, dried, and crystallised from alcohol; m. p. 242—243° (1·2 g., 70%) (Found C, 57·0; H, 3·9; N, 7·7; S, 9·1. $C_{17}H_{14}O_5N_2S$ requires C, 57·0; H, 3·9; N, 7·8; S, 9·0%).

5-(3′ : 5′-Dinitro-4′-hydroxybenzyl)hydantoin.—To concentrated nitric acid (800 ml.; *d* 1·42), maintained at 25—30°, finely powdered 5-(4′-hydroxybenzyl)hydantoin (240 g.) was slowly added with mechanical stirring, which was continued for 2 hours after the end of the addition; the mixture was then poured into water (4 l.), and the crystalline material filtered off and dried at 100°; m. p. 235—236° (decomp.) (270 g.; 80%). It recrystallised from glacial acetic acid as yellow prisms, m. p. 240° (decomp.) (Found: C, 40·8; H, 2·6; N, 18·5. Calc. for $C_{10}H_8O_7N_4$: C, 40·5; H, 2·7; N, 18·9%).

The above dinitro-compound (200 g.) in water (800 ml.) was treated with sodium carbonate (40 g.) in aqueous solution and was converted into its *toluene-p-sulphonyl* ester by treatment with finely ground toluene-*p*-sulphonyl chloride (115 g.), which was added portionwise with stirring until the reaction mixture became colourless. After cooling, the mixture was filtered and the product washed with 2N-sodium carbonate solution to remove unchanged starting material, and then with water. The ester was dried at 60—70°, and crystallised from glacial acetic acid as white prisms, m. p. 218° (180 g.) (Found: C, 45·8; H, 3·2; S, 6·9; N, 12·6. $C_{17}H_{14}O_9N_4S$ requires C, 45·3; H, 3·1; S, 7·1; N, 12·5%).

5-(3′ : 5′-Dinitro-4′-p-methoxyphenoxybenzyl)hydantoin.—(1) The tosyl ester (200 g.) and quinol monomethyl ether (200 g.) were dissolved in pyridine (1500 ml.), and the mixture heated under reflux for 1½ hours. The pyridine was then removed in a vacuum, and the residual gum dissolved in hot glacial acetic acid (800 ml.); water (1 l.) was added, and the product allowed to crystallise. It was

filtered off, thoroughly washed with water, and dried at 100° (148 g.; 83%). Recrystallisation from aqueous acetic acid afforded bright yellow needles, m. p. 235° (decomp.) (Found : C, 50·75; H, 3·8; N, 13·9. $C_{17}H_{14}O_8N_4$ requires C, 50·7; H, 3·5; N, 13·9%). (2) 5-(3′ : 5′-Dinitro-4′-hydroxybenzyl)-hydantoin (20 g.) and toluene-*p*-sulphonyl chloride (14 g.) were dissolved in pyridine (50 ml.), and the solution refluxed for ten minutes. Quinol monomethyl ether (20 g.) in pyridine (20 ml.) was added, and the mixture refluxed for one hour. After cooling, the product was isolated as in (1) (15·2 g.; 56%).

When the above *diphenyl ether* (2 g.) was dissolved in liquid ammonia (20 ml.), and the solution set aside overnight and then evaporated, the residue crystallised from glacial acetic acid as bright yellow prisms, m. p. 289—290° (1·3 g.), and was found to be 5-(3′ : 5′-*dinitro*-4′-*aminobenzyl*)*hydantoin* (Found : C, 40·6; H, 3·4; N, 23·4. $C_{10}H_9O_6N_5$ requires C, 40·7; H, 3·1; N, 23·7%). The *triacetyl* derivative was prepared by refluxing the compound (2 g.) with acetic anhydride (10 ml.) and concentrated sulphuric acid (2 drops) for 10 minutes. It crystallised from aqueous acetic acid; m. p. 206° (2g.) (Found: C, 45·5; H, 4·0; N, 16·9. $C_{16}H_{15}O_9N_5$ requires C, 45·6; H, 3·6; N, 16·6%). From the mother-liquors, a small amount of *diacetyl* derivative crystallised as yellow lances, m. p. 208° (Found : C, 44·3; H, 3·4; N, 18·3. $C_{14}H_{13}O_8N_5$ requires C, 44·3; H, 3·4; N, 18·5%).

5-(3′ : 5′-*Di-iodo*-4′-p-*methoxyphenoxybenzyl*)*hydantoin*.—The dinitro-compound (50 g.), dissolved in glacial acetic acid (225 ml.), was reduced in an autoclave at 80° and 80 atm. pressure with palladised charcoal (5 g.) as catalyst. The solution, after removal of catalyst by filtration, was evaporated in a vacuum to a gum, and the residue dissolved in phosphoric acid (400 ml.). This solution was added dropwise to a cooled, stirred solution of sodium nitrite (20 g.) in concentrated sulphuric acid (400 ml.). One hour after the end of the addition the tetrazonium salt solution was slowly added to a vigorously stirred solution of potassium iodide (55 g.) and iodine (55 g.) in water (900 ml.). A vigorous evolution of gas took place and a brown tarry precipitate was deposited. After being kept overnight, the solid was filtered off and purified either by successive washings with boiling 10% sodium iodide solution or by treatment with a large excess of cold 5% sodium hydrogen sulphite solution. The crude brown solid crystallised from glacial acetic acid as brown crystals, m. p. 150° to resolidify and remelt at 213° (36·5 g.; 52%).

The substance was further purified by passage of an acetone solution down a column of active alumina and precipitation of the product by addition of water to the filtrate. The solid recrystallised from glacial acetic acid as minute white platelets, m. p. 213—214° (Found : C, 36·7; H, 2·8; N, 5·0; I, 44·9. $C_{17}H_{14}O_4N_2I_2$ requires C, 36·2; H, 2·5; N, 4·95; I, 45·0%).

Characterisation of 5-(3′ : 5′-*Diamino*-4′-p-*methoxyphenoxybenzyl*)*hydantoin*.—The dinitro-compound (1 g.) was reduced in acetic acid solution exactly as described above, and the residue after removal of the solvent was taken up in acetic anhydride (15 ml.). The mixture was heated just to boiling and kept overnight; a white solid was deposited, and this was filtered off and recrystallised from aqueous "Cellosolve"; white prisms, m. p. 193—194° (0·64 g.). Elementary analysis identified it as the *triacetyl* derivative (Found : C, 58·4; H, 5·3; N, 11·9. $C_{23}H_{24}O_7N_4$ requires C, 59·0; H, 5·1; N, 11·9%).

The dinitro-compound (2 g.) and palladised charcoal (0·5 g.), suspended in glacial acetic acid (40 ml.), were shaken in an atmosphere of hydrogen until the uptake of the latter was complete. The catalyst was filtered off and the residue, after removal of the solvent in a vacuum, was dissolved in a little alcohol. Hydrogen chloride was passed in, and the *monohydrochloride* crystallised out as white prisms, m. p. 245° (decomp.) (1·7 g.; 90%) (Found : C, 53·6; H, 5·2; N, 15·1; Cl, 8·75. $C_{17}H_{19}O_2N_4Cl$ requires C, 54·0; H, 5·0; N, 14·8; Cl, 9·35%).

2 : 4-*Dinitrophenylpyridinium Salt of* 5-(3′ : 5′-*Dinitro*-4′-*hydroxybenzyl*)*hydantoin*.—1-Chloro-2 : 4-dinitrobenzene (2·0 g.) was refluxed in anhydrous pyridine (5 ml.) for 2 hours with 5-(3′ : 5′-dinitro-4′-hydroxybenzyl)hydantoin (2·96 g.). The hot reaction mixture was diluted with boiling water (30 ml.), treated with charcoal, and filtered through kieselguhr. The filtrate on cooling deposited orange-red needles, m. p. 244° (1·65 g.; 30%), which were recrystallised from either water or methyl cyanide (Found : N, 18·5. $C_{21}H_{15}O_{11}N_7$ requires N, 18·2%). The *salt* could be sublimed at 220° in high vacuum but gave neither a chloroplatinate nor a diphenyl ether under the usual conditions.

N-(2 : 6-*Dinitro*-4-5′-*hydantoinylmethylphenyl*)*pyridinium Toluene*-p-*sulphonate*.—5-(3′ : 5′-Dinitro-4′-toluene-*p*-sulphonyloxybenzyl)hydantoin (4·5 g.) was dissolved in anhydrous pyridine (20 ml.) and kept at room temperature for 10 minutes. Addition of ether caused precipitation of a white hygroscopic solid (3·8 g.; 76%), which could be crystallised from ethyl alcohol but was very deliquescent on exposure to air. The compound gave a *chloroplatinate*, m. p. 219°, from aqueous ethyl alcohol (Found : N, 12·2; Pt, 16·7. $C_{30}H_{24}O_{12}N_{10}Cl_6Pt$ requires N, 12·4; Pt, 17·3%).

The above toluenesulphonate (0·5 g.) was dissolved in cold alcohol and 2 : 4-dinitrophenol (0·18 g.) was added. Slow addition of ether precipitated a solid which was filtered off and washed with ether. The product, which was the 2 : 4-dinitrophenoxide corresponding to the above toluene-*p*-sulphonate, rapidly took up moisture on exposure to air. On treatment with chloroplatinic acid it gave the above chloroplatinate.

The above quaternary 2 : 4-dinitrophenoxide (0·27 g.) was boiled for one hour in pyridine (3 ml.) with quinol monomethyl ether (0·19 g.). The cooled solution was diluted with water, acidified, and extracted with ethyl acetate. The extract was washed, dried ($MgSO_4$), and evaporated to dryness. The residue crystallised from aqueous acetic acid as small yellow prisms, m. p. 231° not depressed on admixture with an authentic sample of 5-(3′ : 5′-dinitro-4′-*p*-methoxyphenoxybenzyl)hydantoin.

5-(3′ : 5′-*Dinitro*-4′-p-*hydroxyphenoxybenzyl*)*hydantoin*.—5-(3′ : 5′-Dinitro-4′-toluene-*p*-sulphonyloxybenzyl)hydantoin (10 g.), quinol (10 g.), and pyridine (100 ml.) were refluxed in an oil-bath at 140° for one hour. The pyridine was completely removed by evaporation in a vacuum and the residual gum was triturated with glacial acetic acid. The soluble portion was filtered off, and the filtrate treated with charcoal and diluted with water. The product was filtered off and crystallised from acetic acid, giving pale yellow prisms, m. p. 242° (4·2 g.; 49%) (Found : C, 49·7; H, 3·4; N, 14·1. $C_{16}H_{12}O_8N_4$ requires C, 49·5; H, 3·1; N, 14·4%). The solid fraction insoluble in acetic acid, crystallised from pyridine–ether, had m. p. above 260° (1·9 g.); it is thought to be the *triphenyl diether* (XII) (Found : C, 46·6; H, 3·1; N, 16·2. $C_{26}H_{18}O_{14}N_8$ requires C, 46·8; H, 2·7; N, 16·8%).

5-(3′ : 5′-*Diamino*-4′-p-*hydroxyphenoxybenzyl*)*hydantoin*.—The above *dinitro*-compound (2 g.), suspended in glacial acetic acid (20 ml.), was reduced with palladised charcoal in the usual manner. The reduction mixture was boiled to redissolve the product which had separated out during reduction and filtered from catalyst. On cooling, the product (1 g.) crystallised as white needles, m. p. 244°, a second crop being obtained from the concentrated mother-liquors. The total yield was 1·4 g. (70%), and the substance was solvated (Found : C, 55·7; H, 5·0; N, 14·4. $C_{16}H_{16}O_4N_4,CH_3{\cdot}CO_2H$ requires C, 55·8; H, 5·2; N, 14·4%).

A benzoyl derivative was prepared as follows : Benzoyl chloride (0·7 g.) was added dropwise to a solution of the material (1 g.) in dry pyridine (10 ml.). After one hour the mixture was poured into a large volume of water, and the precipitated oil induced to crystallise by scratching. The separated solid crystallised from ethyl alcohol as cream needles, m. p. 252—253° (decomp.) (0·8 g.). Elementary analysis identified it as the *dibenzoyl* derivative (Found : C, 67·5; H, 4·3; N, 10·1. $C_{30}H_{24}O_6N_4$ requires C, 67·2; H, 4·5; N, 10·4%).

5-(3′ : 5′-*Di-iodo*-4′-p-*hydroxyphenoxybenzyl*)*hydantoin* (3 : 5-*Di-iodothyroninehydantoin*).—To a mixture of glacial acetic acid (135 ml.) and 57% hydriodic acid (135 ml.), the methoxy-compound (45 g.) was added, and the whole heated gently under reflux. All quickly went into solution, and after about 10 minutes the product began to crystallise. At the end of one hour the mixture was allowed to cool and the white solid was filtered off (38·3 g.; 85%). It was recrystallised with some difficulty from aqueous "Cellosolve", and the decomposition temp. varied with different batches from 228° to 245° (Found : C, 35·0; H, 2·3; N, 4·9. $C_{16}H_{12}O_4N_2I_2$ requires C, 35·0; H, 2·2; N, 5·1%).

3 : 5-*Di-iodothyronine*.—The foregoing *hydantoin* (30 g.) was dissolved in 2N-sodium hydroxide solution (600 ml.), and the solution gently heated under reflux in a stainless-steel pot for 15 hours. After cooling, the solution was acidified with glacial acetic acid, and after some hours' standing the precipitated solid was filtered off and dissolved in ethyl alcohol (300 ml.) containing a little concentrated hydrochloric acid (50 ml.). The boiling solution was treated with charcoal, filtered, and diluted with an equal volume of boiling water; then a boiling saturated solution of sodium acetate was added (*ca.* 200 ml.) until the solution was alkaline to Congo-red paper. On standing, beautiful silver shining plates were deposited (19·7 g.; 69%), m. p. 256° (Found : C, 33·0; H, 3·0; N, 2·6; I, 45·1, 47·2. Calc. for $C_{15}H_{13}O_4NI_2$: C, 34·3; H, 2·5; N, 2·7; I, 48·3%. Calc. for $C_{15}H_{13}O_4NI_2,H_2O$: C, 33·15; H, 2·8; N, 2·6; I, 46·8%).

Thyroxine.—To a solution of 3 : 5-di-iodothyronine (10·5 g.) in concentrated ammonia (*d* 0·91; 100 ml.), a solution of iodine in potassium iodide (1·85N; 43·2 ml.) was added dropwise with vigorous stirring. Stirring was continued for one hour after the end of the addition, and the mixture was then kept in the refrigerator overnight. The ammonium salt was filtered off, and redissolved in alcohol containing a little 2N-sodium hydroxide solution. Acidification with acetic acid precipitated the thyroxine, which was recrystallised by solution in ethyl alcohol (500 ml.) containing concentrated hydrochloric acid (20 ml.) and reprecipitation as minute white crystals on addition of a saturated solution of sodium acetate until the solution was alkaline to Congo-red. The thyroxine was filtered off, washed with alcohol and ether, and dried at 100° (11·2 g.; 73%), m. p. 233—234° (decomp.) (Found: C, 23·15; H, 1·8; N, 1·8; I, 62·2, 64·5. Calc. for $C_{15}H_{11}O_4NI_4$: C, 23·2; H, 1·4; N, 1·8; I, 65·4%).

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